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Hiding in Plain Sight: Molecular Genetics Applied to Giant Congenital Melanocytic Nevi

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Large and giant congenital melanocytic nevi are rare malformations that offer surprising insight into prenatal and postnatal acquisition of nevi of any size, central and peripheral nervous system development, and melanomagenesis. In this issue, Charbel *et al.* demonstrate the use of highly sensitive detection techniques for recurrent but difficult-to-detect mutations in *NRAS* and *BRAF*. It is now possible to systematically add a molecular qualifier to distinguish lesions that had once been considered to be equivalent based on the single visual parameter of size. These findings help to elucidate the pathophysiology of congenital melanocytic nevi and their predisposition to malignancy.

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Nosology of large and giant congenital melanocytic nevi

Congenital melanocytic nevi (CMN) are malformations resulting from the faulty development of melanocyte progenitors in the embryo or fetus, and they are composed ultimately of an abnormal mixture of skin cellular elements. These pigmented hamartomas occupy sharply defined areas along the epidermal–dermal junction that range from a few millimeters in diameter to large swathes of the body, limbs or head. In the larger forms, CMN (single or multiple) often extend vertically into the deeper dermis and more rarely into the hypodermis or even subcutaneous tissues. The first descriptions of children with large CMN date from observations recorded by the French Count of Buffon in 1777, but the incidence of CMN seems to be independent of ethnic factors.

CMN have been classified historically according to their predicted largest diameter in adulthood, as if they were circular (predicted adult size (PAS), as they enlarge proportionately to the child's growth). Until recently, other qualifiers had not systematically been taken into account. CMN measuring 40 cm or larger in PAS are referred to as ''giant'' nevi, according to the most recent and complete classification system (Krengel *et al.*, 2013). This is intended to promote an international standard in phenotyping by including additional criteria such as pilosity, color heterogeneity, rugosity, and the presence of nodular growths, with charts for predicting PAS according to body site and photographic examples. Small (<1.5 cm PAS) CMN occur in more than 1 in 100 births. Larger CMN (Figure 1a) form a much rarer subset, with prevalence estimated at around 1 in 20,000 to 50,000 births as a function of size. Treatment options in the year 2014 remein exclusively surgical.

The differential diagnosis of small and medium CMN includes smooth muscle hamartoma or Becker's nevus, mastocytoma, variants of dermal melanocytosis, and café-au-lait macules. Larger CMN have been confused with pigmented plexiform neurofibromas. Histologic evaluation, dermoscopic evaluation, and the development of typical CMN features over time may clarify the diagnosis. However, molecular characterization promises to be an important additional criterion in phenotyping even the most easily diagnosed lesions and in teasing prognostic factors for syndromic features such as symptomatic neurocutaneous melanocytosis or malignant melanoma. Sensitive molecular diagnoses, such as those most recently developed in this issue of *JID* by Charbel *et al.* (2014), may soon augment the diagnostic and therapeutic arsenal.

''Satellite'' is a term used commonly to describe small or medium CMN, or those that appear postnatally (''tardive'' nevi) in the presence of a large/giant CMN. Both semantically and molecularly, it is more accurate to refer to ''disseminated'' nevi (Kinsler *et al.*, 2013). These disseminated CMN may be present at birth and/or may increase to significant numbers over the first few years of life. Occasionally, a single largest CMN cannot be considered to be the principal malformation among the many, in which case the child is said to have ''multiple medium'' CMN. This presentation correlates with an increased predisposition to neurological abnormalities, as are greater satellite numbers and PAS>20 cm (large and giant CMN; Shah, 2010). Contrary to a common interpretation of the earliest reports of such correlations, there is no discrete biological cut-off as to how many additional disseminated CMN predispose to neurological symptoms or melanoma.

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Clinical Implications

- Gain-of-function somatic mutations in *NRAS* at Q61 have been found in large and giant congenital melanocytic nevi (CMN), but mutant alleles can be difficult to detect.
- Gain-of-function somatic mutations in either *BRAF* at V600 or *NRAS* Q61 have been found in small and medium CMN.
- The principal CMN harbors the same mutation as found in samples from disseminated nevi or complications such as melanoma or central nervous system anomalies of the patient, implying their common origin.

Syndromic CMN

Neurocutaneous melanocytosis, cited in earlier literature as neurocutaneous melanosis (NCM), is characterized by abnormal aggregations of nevomelanocytes within the central nervous system (CNS) of an estimated 5–15% of patients with the larger forms of CMN, or multiple medium-sized CMN. Neurological signs may include hydrocephalus, epilepsy, arachnoid cysts, tethered spinal cord, Dandy–Walker malformation (cerebellar vermis hypoplasia), developmental delay, and a number of rarer CNS tumors (Kinsler *et al.*, 2013). True melanosis, through accumulation of melanin in CNS neurons or glia, may also occur in association with CMN, but further neuropathological studies need to be undertaken for this to be conclusive.

Melanoma develops in an estimated 1–2% of pre-pubertal patients with large CMN or NCM, on the order of 10,000 times more often than the incidence among the general population of children under the age of 10, based on registry data from the SEER (Surveillance, Epidemiology, and End Results) program of the US National Cancer Institute, 1975–2000. CMN-associated melanoma may be cutaneous, usually within the malformation, but it is often extracutaneous, with some predilection for the CNS. Other malignancies such as liposarcomas, rhabdomyosarcomas, and peripheral nerve sheath tumors have also been described in association with large CMN. Rapidly growing 'proliferative nodules' within the CMN can mimic melanoma but often show benign features on closer examination (Phadke *et al.*, 2011).

Molecular basis of nevus formation

Both CMN and acquired melanocytic nevi are associated exclusively with somatic mutations in intracellular proteins of the microtubule-associated protein kinase (MAPK) signal transduction pathway (Figure 1b). In some series of CMN, only a recurrent mutation in the *NRAS* gene at codon 61 has been described, transforming the glutamine (Q) to lysine (K) or arginine (R) (Kinsler *et al.*, 2013, and references therein), but many others have described a single hotspot mutation in *BRAF* (V600E) as well (Dessars *et al.*, 2009; Phadke *et al.*, 2011)—as is found commonly in adult-onset melanoma. All of the identified

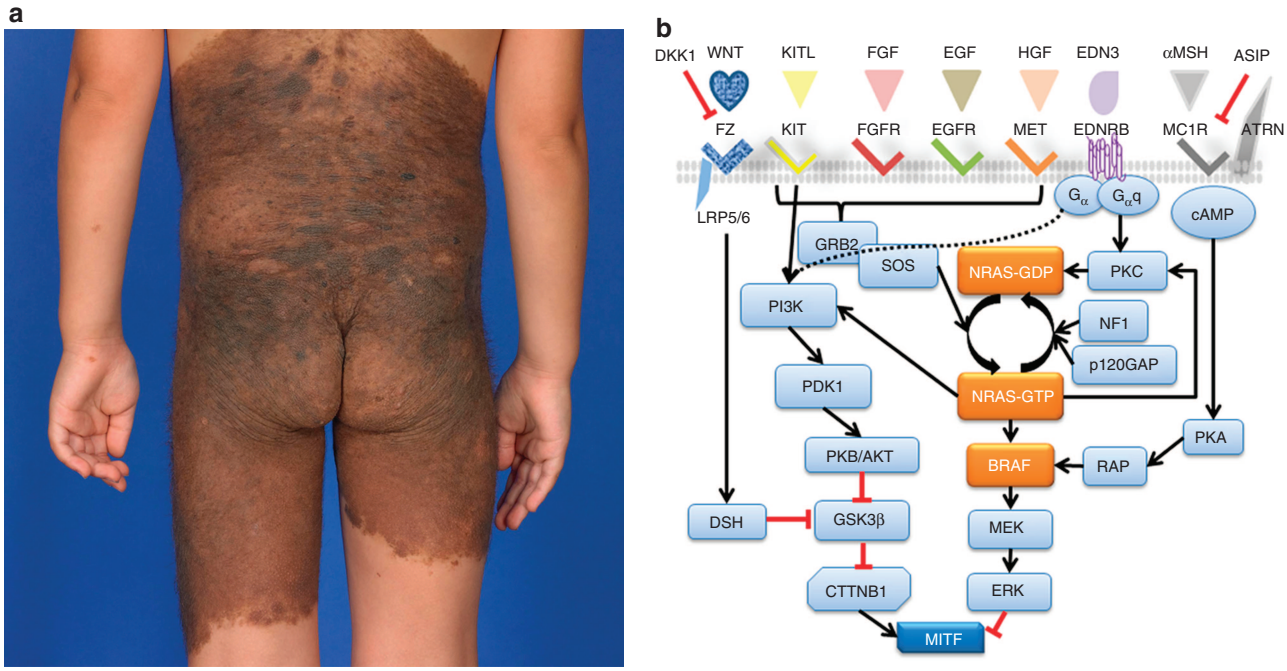

Figure 1. Clinical variablity in large CMN may be due to the many potential modifiers of a mosaic *NRAS* or *BRAF* gain-of-function genotype. (**a**) A 5-year-old girl with a typical giant CMN of the middle and lower back, flanks, abdomen, genitogluteal region, and upper thighs. After two years' follow-up, she has no other syndromic features. Image reprinted with written permission from the family. (**b**) *BRAF*, mutated at V600 in exclusively small-to-medium-sized CMN, and *NRAS*, mutated at Q61 preferentially in large or giant-sized CMN (see Charbel *et al.* 2014), are at the nexus of multiple signaling networks depicted in this cartoon, that are important for melanoblast proliferation and melanocyte differentiation. This nexus coordinates the convergence of signals from receptor tyrosine kinase and G-protein-coupled receptors on not only MAPK-ERK but also PI3K-AKT and other target pathways, to lead to transcriptional modifications.